nivolumab, and pembrolizumab). The 2 terminated studies (both for idelalisib) were stopped owing to significant safety concerns. One product (ponatinib) was temporarily pulled from the market, with the FDA requiring further studies, and a risk evaluation and mitigation strategy; however, the PMR clinical study eventually resumed and was completed. One ongoing trial (for olaparib) was released as a PMR by the FDA. None of the pending or ongoing studies are behind their original schedules as posted in the FDA’s PMR database.

**Discussion** | Recently, the FDA has been criticized for its oversight of PMR clinical studies.  
The agency has come under fire for failure to penalize sponsors for PMR clinical studies completed late. Our own review of PMR clinical studies for novel oncology drug products granted AA within the last 6 years found that no studies were behind their original schedules. However, PMR studies identified serious safety concerns in 2 incidents that resulted in changes to the labeling for both products (idelalisib and ponatinib). In addition, our analysis identified 3 instances (20%) where confirmatory PMR clinical studies for drugs granted AA failed to meet their primary efficacy end points. To date, none of these 3 drugs have been pulled from the market. These examples underscore the importance of collecting the additional clinical safety and efficacy data outlined in the PMRs and the need for collaborative efforts between the FDA, sponsors, and investigators.

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**Concept and design:** Both authors.

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**Drafting of the manuscript:** Both authors.

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**References:**


**Total Costs of Chimeric Antigen Receptor T-Cell Immunotherapy**  
In 2017, the US Food and Drug Administration approved the drugs tisagenlecleucel (Kymriah; Novartis) and axicabtagene ciloleucel (Yescarta; Kite Pharma) as the first chimeric antigen receptor T-cell (CAR-T) immunotherapies. Treatment with tisagenlecleucel has been priced at $475 000 and axicabtagene ciloleucel at $373 000; however, these prices are for the drug products alone and do not account for the costs associated with leukapheresis, lymphodepletion therapy, and the adverse effects of CAR-T immunotherapy. These costs are not negligible as 43 patients (44%) who received tisagenlecleucel in clinical trials required stays in the intensive care unit for cytokine release syndrome (CRS). In this study, we estimated the total costs of CAR-T immunotherapy, including nondrug costs, using publicly available data.

**Methods** | The institutional review board at the University of Pittsburgh deemed this study exempt. We divided the potential outcomes of patients selected for CAR-T immunotherapy into 11 scenarios, accounting for the receipt of treatment, development of CRS, and response to CAR-T immunotherapy (Figure). We calculated the probabilities of each scenario using input probabilities from the Food and Drug Administration Advisory Committee briefing document for tisagenlecleucel,1 the preliminary results of the Determine Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-cell ALL (Acute Lymphoblastic Leukemia) (ELIANA) trial,2 and the Food and Drug Administration-approved label for axicabtagene ciloleucel.3 To calculate the physician costs for leukapheresis and for administration of lymphodepletion therapy and CAR-T immunotherapy, we used the 2017 Medicare Physician Fee Schedule rates; facility costs were calculated using the 2017 Medicare Hospital Outpatient Prospective Payment System amounts. Costs of drugs other than CAR-T drugs were based on 2017 Medicare Part B payment limits. To calculate the facility costs of hospitalizations for CRS, we used estimates from the Healthcare Cost and Utilization Project and from published studies; physician costs were calculated as 26% of facility costs. All estimates were inflated to 2017 US dollars using the Consumer Price Index for Medical Care.

To estimate the mean expected cost per patient treated, we added up the expected costs of the drug product in each scenario and its expected probability and then divided the sum by the probability of being treated. Because Novartis, the manufacturer of tisagenlecleucel, offered to waive the costs of the drug for patients who do not demonstrate a response to treatment after 1 month, we estimated the costs of tisagenlecleucel with and without refunds for individuals with no treatment response.

**Results** | As the Table shows, the total costs of treatment with tisagenlecleucel per patient treated range from $478 777 for those without CRS to $531 823 for those with severe CRS (CRS grade ≥3). The mean expected cost is $510 963, which decreases to $432 131 under the outcomes-based pricing arrangement. The mean expected cost of axicabtagene ciloleucel per
The patient treated is $402,647. With approximately 600 US patients eligible for tisagenlecleucel every year, the $432,131 estimate would translate into annual expenditures of $259 million. With 7500 US patients annually eligible for axicabtagene ciloleucel, the total expenditures would be more than $3 billion.

Discussion | To our knowledge, this study provides the first estimates of the total costs of CAR-T immunotherapy in the United States; these estimates are consistent with those previously calculated for the United Kingdom. Although our study did not examine the benefits associated with CAR-T immunotherapy and hence does not provide estimates of cost-effectiveness, it nevertheless has important implications.

One could argue that the nondrug costs associated with CAR-T immunotherapy are negligible when compared with drug costs, as the former represent 7% of total costs. However, in absolute terms, these nondrug costs are $30,000 to $36,000 for the average patient and as high as $56,000 for those...

Table. Estimated Total Costs and Mean Expected Costs per Patient for Chimeric Antigen Receptor T-Cell Immunotherapies

<table>
<thead>
<tr>
<th>Treatment Scenario</th>
<th>Total Cost, $a</th>
<th>Tisagenlecleucel</th>
<th>Axicabtagene Ciloleucel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not treated</td>
<td>1207</td>
<td>1207</td>
<td>1207</td>
</tr>
<tr>
<td>Treated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>478 777</td>
<td>478 777</td>
<td>377 253</td>
</tr>
<tr>
<td>No response</td>
<td>502 464</td>
<td>502 464</td>
<td>400 940</td>
</tr>
<tr>
<td>Grade 1-2 CRS, received no tocilizumab</td>
<td>504 276</td>
<td>29 276</td>
<td>404 564</td>
</tr>
<tr>
<td>Grade 1-2 CRS, received tocilizumab</td>
<td>530 011</td>
<td>530 011</td>
<td>415 429</td>
</tr>
<tr>
<td>Grade ≥3 CRS, received no tocilizumab</td>
<td>531 823</td>
<td>531 823</td>
<td>415 053</td>
</tr>
<tr>
<td>Grade ≥3 CRS, received tocilizumab</td>
<td>510 963</td>
<td>510 963</td>
<td>402 647</td>
</tr>
</tbody>
</table>

Mean expected costs per patient treated: 510 963

Abbreviation: CRS, cytokine release syndrome.

a All costs are expressed in 2017 US dollars.
b Under the outcomes-based pricing agreement announced by Novartis, the manufacturer of tisagenlecleucel, drug costs would be waived for those patients who do not respond to treatment within 1 month of administration.

c A CRS grade of 3 or greater represents severe CRS.
with severe CRS; these costs are equivalent to the costs of many of today’s most expensive medications. Moreover, under the proposed outcomes-based pricing arrangement, nondrug costs are not refunded for patients who do not demonstrate a response to treatment. Payers and the public must understand that only the costs borne by the manufacturer, but not the total costs of CAR-T immunotherapy, will be reimbursed for those who display no treatment response.

As the number of patients eligible for CAR-T immunotherapy and other expensive therapies increase, accurately measuring and accounting for the associated nondrug costs will be important when assessing the treatment’s true costs and value and when negotiating pricing arrangements.

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Study concept and design: Hernandez, Gellad.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Hernandez. Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Hernandez.

Administrative, technical, or material support: Hernandez.

Study supervision: Gellad.

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Assessment of Electronic Alert to Reduce Overuse of Granulocyte Colony-Stimulating Factor in Patients Hospitalized for Febrile Neutropenia

Prophylactic granulocyte colony-stimulating factors (G-CSFs) reduce the risk of febrile neutropenia (FN).1 Owing to the efficacy of prophylactic G-CSF, multiple studies have evaluated the therapeutic use of G-CSF during FN; however, no difference in overall mortality or infection-related mortality was observed.2 American Society of Clinical Oncology (ASCO) guidelines state that “GCSFs should not be used for the treatment of FN. However, GCSFs can be considered in patients at high-risk for complications.”3 Despite these guidelines, up to 62% of patients with FN receive G-CSF.3 Our objective was to evaluate the efficacy of an alert in the electronic health record (EHR) in reducing the therapeutic use of G-CSF.

Methods | This study was conducted from February 12, 2014, to April 12, 2016, at an academic multisite hospital where all orders are entered electronically. Beginning March 12, 2015, an EHR alert was triggered by the entry of an order for filgrastim or tbo-filgrastim. Clinicians were prompted to select an indication from a dropdown menu. If FN was selected, ASCO guidelines were displayed, and clinicians were required to select the indication.1 We compared the use of G-CSF the year prior to with the use of G-CSF the year after the alert was implemented. The study was approved by the Columbia University Medical Center and Well Cornell Medical Center Institutional Review Boards, who waived patient consent, as the data were deidentified.

Patients were eligible if they had cancer and were hospitalized with FN. Covariates included age, sex, cancer type, and insurance. Patients were categorized as high risk if they were older than 65 years of age or had sepsis, pneumonia, or an invasive fungal infection. All analyses were conducted with SAS, version 9.4 software (SAS Institute Inc). P < .05 (2-sided) was considered significant.

Results | We identified 683 eligible patients, resulting in 880 unique admissions for FN (438 women and 442 men; mean [SD] age, 59.7 [15.8] years); 237 admissions (26.9%) were categorized as low risk (Table). There was no change in the use of G-CSF use before and after the alert (60 of 544 admissions [11.0%] vs 46 of 336 admissions [13.7%]; P = .61). Among the low-risk admissions, the use of G-CSF increased from 27 of 121 (22.3%) prior to the EHR alert to 40 of 116 (34.5%) after (P = .04) (Figure). Among the 643 high-risk admissions, the use of G-CSF did not change (139 of 423 [32.9%] vs 68 of 220 [30.9%]; P = .62). The most common indication selected was treatment of FN (44 of 108 admissions [40.7%]). However, prophylaxis was selected 20.4% of the time (22 of 108 admissions) (Table).

Discussion | We found that approximately one-third of patients hospitalized with FN received G-CSF, and the level of use did not decrease after the implementation of an EHR alert.

Letters

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